The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 14, 2024 VOL. 390 NO. 11

A Cell-free DNA Blood-Based Test for Colorectal Cancer Screening

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ABSTRACT

BACKGROUND

Colorectal cancer is the third most diagnosed cancer in adults in the United States. Early detection could prevent more than 90% of colorectal cancer–related deaths, yet more than one third of the screening-eligible population is not up to date with screening despite multiple available tests. A blood-based test has the potential to improve screening adherence, detect colorectal cancer earlier, and reduce colorectal cancer–related mortality.

METHODS

We assessed the performance characteristics of a cell-free DNA (cfDNA) blood-based test in a population eligible for colorectal cancer screening. The coprimary outcomes were sensitivity for colorectal cancer and specificity for advanced neoplasia (colorectal cancer or advanced precancerous lesions) relative to screening colonoscopy. The secondary outcome was sensitivity to detect advanced precancerous lesions.

RESULTS

The clinical validation cohort included 10,258 persons, 7861 of whom met eligibility criteria and were evaluable. A total of 83.1% of the participants with colorectal cancer detected by colonoscopy had a positive cfDNA test and 16.9% had a negative test, which indicates a sensitivity of the cfDNA test for detection of colorectal cancer of 83.1% (95% confidence interval [CI], 72.2 to 90.3). Sensitivity for stage I, II, or III colorectal cancer was 87.5% (95% CI, 75.3 to 94.1), and sensitivity for advanced precancerous lesions was 13.2% (95% CI, 11.3 to 15.3). A total of 89.6% of the participants without any advanced colorectal neoplasia (colorectal cancer or advanced precancerous lesions) identified on colonoscopy had a negative cfDNA blood-based test, whereas 10.4% had a positive cfDNA blood-based test, which indicates a specificity for any advanced neoplasia of 89.6% (95% CI, 88.8 to 90.3). Specificity for negative colonoscopy (no colorectal cancer, advanced precancerous lesions, or nonadvanced precancerous lesions) was 89.9% (95% CI, 89.0 to 90.7).

CONCLUSIONS

In an average-risk screening population, this cfDNA blood-based test had 83% sensitivity for colorectal cancer, 90% specificity for advanced neoplasia, and 13% sensitivity for advanced precancerous lesions. (Funded by Guardant Health; ECLIPSE ClinicalTrials.gov number, NCT04136002.)

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N Engl J Med 2024;390:973-83.
DOI: 10.1056/NEJMoa2304714

Colorectal cancer is the third most diagnosed cancer and second leading cause of cancer-related death in adults in the United States.[1,2] The lifetime risk of colorectal cancer in the United States is approximately 4%, with 53,000 persons expected to die from the disease in 2024.[1,2] Earlier detection of colorectal cancer affects overall survival; 5-year survival is 91% among persons with localized disease as compared with 14% among those with metastatic disease.[1,2] Asymptomatic screening reduces the incidence of colorectal cancer and related deaths and is uniformly recommended by leading professional societies, including the U.S. Preventive Services Task Force (USPSTF), the U.S. Multi-Society Task Force on Colorectal Cancer, and the American Cancer Society (ACS).[3-7] Numerous screening options are available, including direct visualization and stool-based tests, but owing to inherent barriers, approximately 59% of eligible persons 45 years of age or older are adherent to screening guidelines,[2] well below the target of 80% set forth by the National Colorectal Cancer Roundtable (established by the Centers for Disease Control and Prevention and the ACS).[8] In addition, 76% of colorectal cancer–related deaths occur in persons who are not up to date with screening.[9] There is a pressing need for screening tests for colorectal cancer that are easier to administer and increase adherence.

Factors contributing to low screening adherence include the time required to perform screening, scheduling challenges, concern over test invasiveness and pain, fear of the test, discomfort or embarrassment associated with endoscopic examinations, lack of insurance coverage, distance from the test provider, and lack of physician recommendation for screening.[10] Incorporating a blood-based test, performed as part of a routine health care encounter, to the existing screening paradigm would provide an additional screening option that is relatively simple to complete, thus improving adherence.[11,12] Here we report the performance of a cell-free DNA (cfDNA) blood-based screening test for colorectal cancer in an average-risk population.

Methods

Study Design

The ECLIPSE (Evaluation of the ctDNA LUNAR Test in an Average Patient Screening Episode) study was designed to evaluate the performance of the cfDNA blood-based test (Shield, Guardant Health) to detect asymptomatic and early-stage colorectal cancer in a screening-relevant population. Eligible persons were enrolled in this prospective, observational, multicenter study at 265 U.S. sites, including primary care and endoscopy centers in academic and community-based institutions (see the Supplementary Appendix, available with the full text of this article at NEJM.org). The study protocol (available at NEJM.org) was approved by a central and site-specific institutional review board (as required). All the participants or their legal representatives provided written informed consent.

Guardant Health funded the study, which was designed by the authors. A contract research organization, Premier Research, gathered and monitored the data. The study statistician (seventh author) analyzed the data and vouches for the completeness and accuracy of the data and for the fidelity of the study to the protocol, along with the first and last authors and two authors employed by Guardant Health (sixth and eighth authors). The first draft of the manuscript was written by an employee of Guardant Health (fifth author) and an employee of a contract research organization, funded by Guardant Health. All the authors reviewed and edited the manuscript and agreed to submit it for publication. Authors not employed by Guardant Health signed clinical advisory agreements with Guardant Health related to the ECLIPSE study design and execution as well as data review and analysis.

Study Population

Eligible persons were 45 to 84 years of age at the time of consent, at average risk for colorectal cancer and undergoing routine screening with colonoscopy. Key exclusion criteria were a history of cancer, a known diagnosis of inflammatory bowel disease, a hereditary predisposition to colorectal cancer, a history of colorectal cancer in a first-degree relative, and recent receipt of screening for colorectal cancer (colonoscopy within the preceding 9 years, positive fecal immunohistochemical test [FIT] or fecal occult blood test within the preceding 6 months, or completion of the multitarget stool DNA test or methylated Septin9 blood test within the preceding 3 years).

CLINICAL PROCEDURES

Participants provided written informed consent and a study blood sample before any medical preparation for colonoscopy. Standard-care screening colonoscopy was preferably performed within 60 days after enrollment (with the date of enrollment considered to be the date that the study blood sample was obtained), but an extended timeline for colonoscopy was allowed owing to procedural delays caused by the coronavirus disease 2019 global pandemic.[13,14] Colonoscopy bowel preparation was prescribed according to the standard of care, with the quality of bowel preparation assessed by the endoscopist for each participant. A completed colonoscopy was defined as visualization of the appendiceal orifice or ileocecal valve with photographic documentation, unless a large lesion or mass prohibited completion. Repeat colonoscopy was permitted, provided that it was for clinical reasons and the repeat procedure was completed within the study window. The size and location of colonoscopy-identified lesions were recorded, and resected lesions were referred for histopathological review. When multiple lesions were referred for review, the most advanced lesion was considered to be the primary lesion for final data analysis (Table S2 in the Supplementary Appendix). Endoscopic and histopathological reports for lesions that were assessed locally as advanced neoplasia (advanced precancerous lesions or colorectal cancer) were centrally reviewed.

PRIMARY AND SECONDARY OUTCOMES

The coprimary outcomes were sensitivity for colorectal cancer and specificity for advanced neoplasia in average-risk participants, 45 to 84 years of age, as compared with the colonoscopy reference standard. The secondary outcome was sensitivity for detection of advanced precancerous lesions. Such lesions were defined as advanced adenoma (tubular adenoma ≥10 mm in the largest dimension, adenoma of any size with villous features, high-grade dysplasia, or carcinoma in situ) or sessile serrated lesions at least 10 mm in the largest dimension. Any advanced colorectal neoplasia was defined as colorectal cancer or advanced precancerous lesions identified on colonoscopy. Any colorectal neoplasia was defined as colorectal cancer, advanced precancerous lesions, or nonadvanced precancerous lesions identified on colonoscopy.

LABORATORY PROCEDURES

Whole-blood samples (30 to 80 ml) were collected in Streck cfDNA blood-collection tubes, shipped at ambient temperatures to the central biorepository, processed to plasma, and stored at −80°C until shipment to the central laboratory for analysis (Guardant Health). All samples were received in the central biorepository and central laboratory masked to clinical findings. Central laboratory remained unaware of the clinical attributes of the participants throughout the entire duration of the study.

The test under assessment is a cfDNA blood-based assay for the detection of colorectal cancer. The panel interrogates cfDNA genomic alterations, aberrant methylation status, and fragmentomic patterns. Results are integrated into a binary "abnormal signal detected" (positive test) or "normal signal detected" (negative test). Result thresholds were locked before analyses of the study samples (see the Supplementary Appendix). Binary results were reported to the contract research organization, where they were associated with the clinical outcomes for analysis.

STATISTICAL ANALYSIS

The coprimary outcomes were sensitivity of the cfDNA blood-based test for colorectal cancer and specificity of the test for advanced neoplasia as compared with reference-standard screening colonoscopy with histopathological diagnosis. For previously approved screening tests for colorectal cancer, the Food and Drug Administration (FDA) has established that sensitivity for colorectal cancer is considered to be acceptable if the lower boundary of the two-sided 95% Wilson confidence interval exceeds 65% and that specificity for advanced neoplasia is considered to be acceptable if the lower boundary of the two-sided 95% Wilson confidence interval exceeds 85%.[15,16] These were the coprimary outcome measures for this study.

For the secondary outcome measure, sensitivity of the cfDNA blood-based test for advanced precancerous lesions was calculated and reported with the corresponding two-sided 95% Wilson confidence interval. Exploratory outcome measures included the prevalence-adjusted positive

predictive value for advanced neoplasia, the negative predictive value for colorectal cancer, and a multiple imputation sensitivity analysis that accounted for missing data (see the Supplementary Appendix). The study was powered for the coprimary outcomes. Other analyses are insufficiently powered, and reported 95% confidence intervals are descriptive. The study sample size was calculated on the basis of a prevalence of colorectal cancer of 0.5 to 0.7%. Target enrollment was 68 evaluable participants with colorectal cancer and 7000 evaluable participants who were negative for advanced neoplasia on colonoscopy. Enrollment continued until the target number of colorectal cancers was reached. Final enrollment as of the data-cutoff date for the primary analysis was 65 evaluable participants with colorectal cancer, which provided the study with 85% power to establish that the sensitivity of the cfDNA blood-based test for colorectal cancer is greater than 65% at a true sensitivity of 82%.

Given that the coprimary specificity outcome was sufficiently powered with 7000 participants who were negative for advanced neoplasia on colonoscopy, the population without a diagnosis of colorectal cancer was randomly sampled to the target sample size of approximately 7000 evaluable participants who were negative for advanced neoplasia on the basis of the expected colonoscopy availability and occurrence of test failure. Sampling was performed with the use of a stratified random approach, such that the age distribution of the selected participants without colorectal cancer followed the 2020 U.S. age distribution.[17] Cohort sampling was completed before sample testing, with age being the only clinical variable considered. The sample of 7000 participants without advanced neoplasia corresponds to a power of at least 80% to establish the coprimary specificity of greater than 85%, under the assumption that the true specificity for advanced neoplasia is at least 86.3%. There was a single interim analysis for futility of the outcome of specificity for advanced neoplasia, which was not met. A separate cfDNA assay in combination with analysis of tumor-specific plasma proteins was independently evaluated in this study population; details are provided in the Supplementary Appendix and protocol. Power calculations for the selection of sample size were based on the use of the Wilson interval. Statistical-power calculations and analyses were conducted with the use of SAS software, version 9.8.

RESULTS

PARTICIPANTS

Between October 2019 and September 2022, a total of 22,877 participants were enrolled, including 65 evaluable participants with colonoscopy-identified colorectal cancer (48 [74%] with confirmed stage I, II, or III disease). A total of 10,193 participants without colorectal cancer were randomly selected from the enrolled participants, for a clinical validation cohort of 10,258 participants. A total of 7861 participants (76.6%) met all inclusion and exclusion criteria, had completed and valid colonoscopy results, had valid cfDNA blood-based test results, and were evaluable for final analysis (Fig. 1). The mean age of the participants in the evaluable cohort was 60 years (range, 45 to 84), and 53.7% were women. With respect to race, 7.1% of the participants were Asian, 11.8% were Black or African American, and 78.5% were White; with respect to ethnic group, 13.3% were Hispanic or Latino (Table 1 and Tables S3 and S4). These demographic characteristics closely mirror the racial and ethnic distribution in the 2020 U.S. Census[17]; details on the representativeness of the study population are provided in Table S10.

COPRIMARY EFFECTIVENESS RESULTS

A total of 54 of 65 participants (83.1%) with colonoscopy-detected colorectal cancer had a positive cfDNA test, and 11 (16.9%) had a negative cfDNA test, which indicates that the cfDNA blood-based test had an overall sensitivity of 83.1% (95% confidence interval [CI], 72.2 to 90.3) (Table 2). The lower boundary of the 95% confidence interval exceeded the acceptance criterion of 65%, as established in other FDA-approved screening tests for colorectal cancer. The cfDNA blood-based test identified 42 of 48 screening-relevant (stage I, II, or III) colorectal cancers (sensitivity, 87.5%; 95% CI, 75.3 to 94.1), including 11 of 17 stage I cancers (sensitivity, 65%; 95% CI, 41 to 83), 14 of 14 stage II cancers (sensitivity, 100%; 95% CI, 78 to 100), and 17 of 17 stage III cancers (sensitivity, 100%; 95% CI, 82 to 100). The test also identified 10 of

10 stage IV colorectal cancers (sensitivity, 100%; 95% CI, 72 to 100). Sensitivity according to stage trended higher with more advanced cancer; however, the small sample did not allow for formal comparison (Fig. S1).

There were no substantial differences in sensitivity for colorectal cancer according to primary tumor location, tumor histologic grade (Table S6), or demographic characteristics of the participants (Table S7). Seven of 65 histopathologically confirmed colorectal cancers had insufficient clinical follow-up to confirm the cancer stage: 5 were malignant polyps for which full cancer staging was not completed (Table S8), and 2 were in participants who were lost to clinical follow-up. The sensitivity of the cfDNA blood-based test in this subgroup was 29% (95% CI, 8 to 64) (2 of 7 cancers). There were no reported serious adverse events related to the blood-collection procedure or reported unanticipated cfDNA assay–related adverse events across the 22,877 enrolled participants (Table S9).

A total of 89.6% of the participants without any advanced colorectal neoplasia (colorectal cancer or advanced precancerous lesions) identified on colonoscopy had a negative cfDNA blood-based test, whereas 10.4% had a positive cfDNA blood-based test, which indicates a specificity for advanced neoplasia of 89.6% (95% CI, 88.8 to 90.3) (Table 2). The lower boundary of the 95%

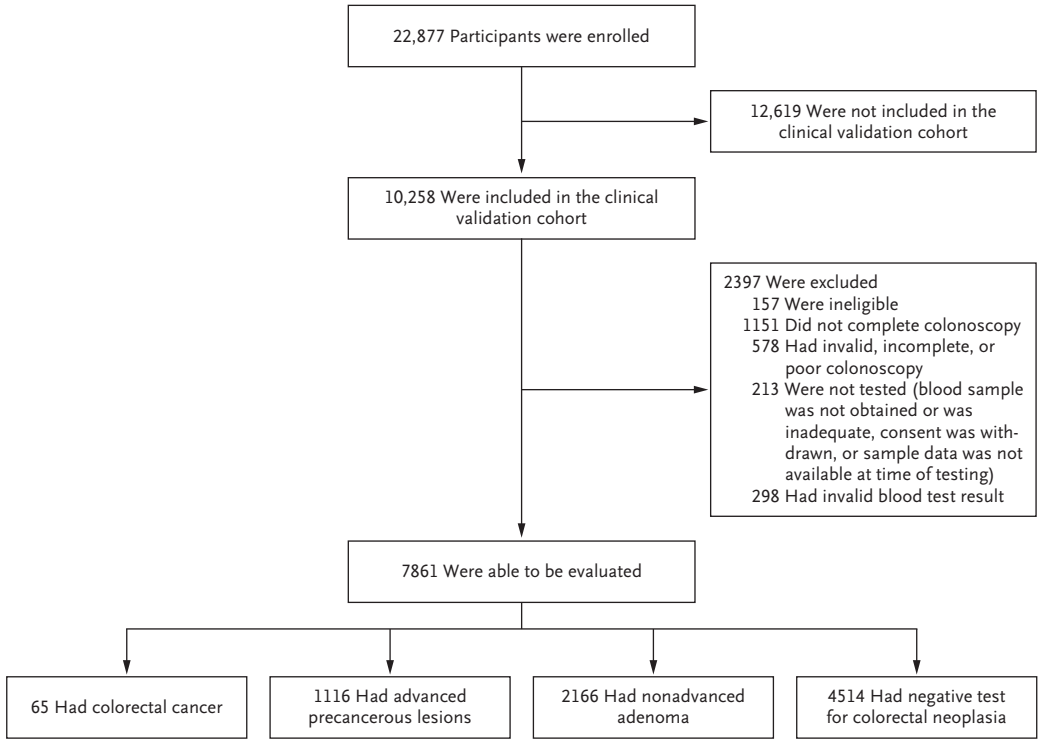

Figure 1. Enrollment and Outcomes.

A total of 22,877 participants were enrolled. Given that the coprimary specificity outcome was sufficiently powered with 7000 participants who were negative for advanced neoplasia on colonoscopy, the population without a diagnosis of colorectal cancer was down-sampled to the target sample of approximately 7000 evaluable participants who were negative for advanced neoplasia on the basis of the expected colonoscopy availability and occurrence of test failure. Sampling was performed with the use of a stratified random approach, such that the age distribution of the selected participants without colorectal cancer followed the 2020 U.S. age distribution. Cohort sampling was completed before sample testing, with age being the only clinical variable considered. Reasons for exclusion are listed in order of priority.

Table 1. Demographic Characteristics of the Participants.*

Characteristic	Enrolled Cohort (N=22,877)	Clinical Validation Cohort (N=10,258)	Evaluable Participants (N=7861)
Age			
Mean — yr	60.8±8.2	60.6±9.1	60.3±9.1
Median (range) — yr	62 (22–90)	60 (45–90)	60 (45–84)
Age group — no. (%)			
45–49 yr	1,881 (8.2)	776 (7.6)	640 (8.1)
50–59 yr	6,414 (28.0)	3877 (37.8)	3055 (38.9)
60–69 yr	11,179 (48.9)	3284 (32.0)	2440 (31.0)
70–79 yr	3,237 (14.1)	2226 (21.7)	1670 (21.2)
≥80 yr	144 (0.6)	95 (0.9)	56 (0.7)
Missing data or other†	22 (0.1)	0	0
Sex — no. (%)			
Female	12,284 (53.7)	5493 (53.5)	4218 (53.7)
Male	10,580 (46.2)	4765 (46.5)	3643 (46.3)
Missing data	13 (0.1)	0	0
Race or ethnic group — no. (%)‡			
American Indian or Alaska Native	53 (0.2)	19 (0.2)	14 (0.2)
Asian	1,867 (8.2)	685 (6.7)	560 (7.1)
Black or African American	2,915 (12.7)	1353 (13.2)	931 (11.8)
Native Hawaiian or other Pacific Islander	50 (0.2)	24 (0.2)	19 (0.2)
White	17,424 (76.2)	7939 (77.4)	6167 (78.5)
Other	441 (1.9)	189 (1.8)	137 (1.7)
Multiple	65 (0.3)	32 (0.3)	23 (0.3)
Missing data	62 (0.3)	17 (0.2)	10 (0.1)
Hispanic or Latino ethnic group — no. (%)‡			
Yes	3,301 (14.4)	1561 (15.2)	1044 (13.3)
No	19,447 (85.0)	8643 (84.3)	6779 (86.2)
Missing data	129 (0.6)	54 (0.5)	38 (0.5)

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding.
† A total of 16 participants had an unknown age, and 6 participants were younger than 45 years of age.
‡ Race or ethnic group was reported by the participant.

confidence interval exceeded the prespecified acceptance criterion of 85%. A total of 89.9% of the participants who had a negative colonoscopy (defined as no colorectal cancer, advanced precancerous lesions, or nonadvanced precancerous lesions identified on colonoscopy) had a negative cfDNA blood-based test, whereas 10.1% of the participants had a positive cfDNA test, which indicates a false positive rate of 10.1% and a specificity for no neoplasia of 89.9% (95% CI, 89.0 to 90.7) (Table 2). Specificity for advanced neoplasia was inversely correlated with age.

SECONDARY OUTCOME ANALYSES

Among 1116 participants with advanced precancerous lesions identified as the most advanced

Table 2. Sensitivity and Specificity of the Cell-free DNA (cfDNA) Blood-Based Test for the Most Advanced Findings on Colonoscopy.*

Variable	Most Advanced Finding on Colonoscopy	cfDNA Blood-Based Test	
		Positive Test	Sensitivity (95% CI)
	no.	*no.*	%
Colorectal cancer			
Any	65	54	83.1 (72.2–90.3)
Stage I, II, or III*	48	42	87.5 (75.3–94.1)
Advanced precancerous lesions†	1116	147	13.2 (11.3–15.3)
			Specificity (95% CI)
Nonadvanced adenomas, nonneoplastic findings, and negative colonoscopy	6680	698	89.6 (88.8–90.3)
Nonneoplastic findings and negative colonoscopy	4514	457	89.9 (89.0–90.7)

* Excluded were 10 stage IV and 7 pathologically confirmed, incompletely staged colorectal cancers.
† Advanced precancerous lesions include advanced adenomas and sessile serrated lesions at least 10 mm in the largest dimension.

Table 3. Expected Diagnostic Yield in a Theoretical Screening Population of 100,000 Average-Risk Persons.*

Colonoscopy Finding	Persons with Finding	Positive cfDNA Blood-Based Test (N=11,049)		Negative cfDNA Blood-Based Test (N=88,951)	
	no.	*no.*	%	*no.*	%
Colorectal cancer	420	349	3.16	71	0.08
Advanced precancerous lesions	10,800	1423	12.88	9,377	10.54
Nonadvanced neoplasia or negative colonoscopy	88,780	9277	83.96	79,503	89.38

* Values were derived from study data extrapolated to a theoretical population of 100,000 patients with the observed prevalence of colorectal cancer of 0.42% and prevalence of advanced precancerous neoplasia of 10.84% in the ECLIPSE study.

lesion on colonoscopy, the cfDNA blood-based test was positive for 147 (13.2%), which indicates a sensitivity for advanced precancerous lesions of 13.2% (95% CI, 11.3 to 15.3) (Table 2). There were no appreciable differences in test sensitivity according to the histopathological features, size, or location of the advanced precancerous lesion.

EXPLORATORY ANALYSES

Among 7861 participants, 11.4% had a positive cfDNA blood-based test. We conducted an analysis in a hypothetical population of 100,000 screening-relevant persons with an observed prevalence of colorectal cancer of 0.42% (Table 3). The positive predictive value of the cfDNA test for detection of colorectal cancer in this population was 3.2%, which indicates a positive likelihood ratio of 7.5. At an observed prevalence of advanced precancerous lesions of 10.8%, the positive predictive value of the cfDNA test for detection of advanced precancerous lesions in this population was 12.9%, which indicates a positive likelihood ratio of 1.2. In this population, the prevalence of no colorectal cancer was 99.6%, and negative predictive value of the cfDNA test was 99.9% (95% CI, 99.9 to 100) (Table 3).

In an analysis that used multiple imputation of missing data and included all 10,101 eligible participants who met the inclusion criteria (Fig. 1), results were generally similar to those

of the primary prespecified analyses (see the Supplementary Appendix). The sensitivity for colorectal cancer was 80.2% (95% CI, 68.7 to 88.2%). Specificity for any advanced neoplasia (advanced precancerous lesions or colorectal cancer) was 89.4% (95% CI, 88.7 to 90.1). Specificity in the participants without any colonoscopy-identified colorectal neoplasia was 89.8% (95% CI, 88.9% to 90.6%). Sensitivity for advanced precancerous lesions was 13.5% (95% CI, 11.4 to 16.0).

DISCUSSION

In this evaluation of a cfDNA blood-based test, Shield, for the detection of colorectal cancer in an average-risk screening population, sensitivity for colorectal cancer was 83%, and specificity for advanced neoplasia was 90%. The lower boundaries of the 95% confidence intervals for sensitivity for colorectal cancer and specificity for advanced neoplasia met the prespecified acceptance criteria as established in other FDA-approved screening tests for colorectal cancer. Sensitivity for advanced precancerous lesions was 13%. The false positive rate of this cfDNA blood-based test was 10.1% (i.e., 10.1% of the patients who did not have any neoplasia on colonoscopy had a positive cfDNA blood-based test).

ECLIPSE was a large-scale study of colonoscopy screening alternatives that evaluated persons 45 to 49 years of age alongside those 50 years of age or older, which is relevant given the USPSTF update to begin average-risk screening at 45 years of age.[3] The generalizability of the study findings is supported by the fact that study sites encompassed 76% of U.S. states (38 of 50), with more than 90% of sites located within community-based health care centers. The study population was racially and ethnically diverse and representative of the U.S. population (Table 1).

There was no apparent unexpected variation in performance among subgroups. Specificity was inversely correlated with age, probably owing to age-specific cfDNA methylation signatures, a trend observed at a greater magnitude with other noninvasive screening tests for colorectal cancer.[15,18-20] The observed performance associations of test sensitivity with age, stage of colorectal cancer, and the size and severity of advanced precancerous lesions are expected. Seven participants with colorectal cancer had insufficient clinical follow-up to determine cancer stage; 71% (5 of 7) had malignant polyps, defined as pT1 lesions or submucosally invasive lesions.[21] The incidence of malignant polyps has increased with the uptake of colorectal cancer screening, and appropriate management after lesion removal is subject to variability influenced by patient-level factors and tumor features, which is reflected in this study.[21,22] According to the protocol, all the participants had to undergo full clinical staging to define disease stage. With malignant polyps, clinical staging is often incomplete, and cases in these persons are typically managed as clinical stage I colorectal cancers. When test performance was evaluated on the basis of clinical stage, sensitivity for clinical stage I colorectal cancer was 55% (95% CI, 35 to 73) (12 of 22 cancers) and sensitivity for clinical stage I, II, or III colorectal cancer was 81% (95% CI, 69 to 90) (43 of 53 cancers).

The sensitivity of this blood-based test for colorectal cancer was 83.1%, whereas reported sensitivity of other noninvasive screening tests ranges from 67.3% (95% CI, 57.1 to 76.5) with FIT[15] and 68% (95% CI, 53 to 80) with the methylated Septin9 test[19] to 93.9% (95% CI, 87.1 to 97.7) with the multitarget stool DNA test.[15] The sensitivity of this blood-based test for advanced precancerous lesions was 13.2% (95% CI, 11.3 to 15.3), whereas reported sensitivity of other noninvasive screening tests ranges from 22% (95% CI, 18 to 24) with the methylated Septin9 test[19] and 23.3% (95% CI, 21.5 to 25.2) with FIT[15] to 43.4% (95% CI, 41.3 to 45.6) with the multitarget stool DNA test.[15]

In average-risk screening, action is taken on the basis of findings of advanced neoplasia, including colorectal cancer and advanced precancerous lesions. Advanced precancerous lesions are considered to be noninvasive, precancerous lesions, and the underlying biologic features of advanced precancerous lesions may result in detection limitations with the current blood-based testing methods that have been developed to detect invasive cancers. Noninvasive detection of advanced precancerous lesions remains a

challenge more broadly, because the most appropriate precancerous target has not been precisely defined and no noninvasive screening test yet approaches the aspirational sensitivity goal of 90%.[23] Ongoing efforts to improve cfDNA detection capabilities and to leverage other blood-based analytes (cell-free RNA, exosomes, and autoantibodies) may lead to sensitivity improvements.[24-26] Specificity of this cfDNA blood-based test for advanced neoplasia was 89.6% (95% CI, 88.8 to 90.3), whereas reported specificity of other noninvasive screening tests range from 79.1% (95% CI, 77.0 to 81.4) with the methylated Septin9 test[19] to 90.6% (95% CI, 90.1 to 91.0) with the multitarget stool DNA test[15] and 94.8% (95% CI, 94.4 to 95.1) with FIT.[15]

Screening programs can improve population-level outcomes but require consideration of multiple factors to be effective.[27] Although one of these factors is the clinical validity or efficacy of the screening test, it is not the sole determinant of clinical effectiveness, the real-world performance of the test.[28] Screening tests must be acceptable, accessible, and person-centered to achieve the maximum participation crucial to provide population benefit.[29-31] Success of a screening program is therefore heavily influenced by adherence. Colonoscopy, the diagnostic reference standard, has the advantage of both identification and removal of precancerous lesions and therefore the ability to detect and prevent colorectal cancer. However, the Nordic-European Initiative on Colorectal Cancer trial highlights how this highly efficacious screening strategy can have its clinical effectiveness hindered by poor real-world adherence.[32] Participant adherence varies considerably among the available colorectal cancer screening methods, with only 59% of screening-eligible persons being up to date with screening and more than 49 million unscreened persons in the United States. Estimates of adherence to blood-based tests are higher than those reported for stool-based tests or direct visualization tests.[3,32-36] Blood-based testing offers an additional option for colorectal cancer screening, in addition to the available stool-based tests, and may improve screening participation and early detection of colorectal cancer.[37,38]

Evaluation of participant adherence to this cfDNA blood-based test in various clinical settings is warranted and is an area of active investigation, especially given that participant adherence is affected by many factors beyond the test availability.[37-41] It is also important to highlight that a screening strategy that uses noninvasive testing requires adherence to the screening test and to the diagnostic colonoscopy in those with positive screening tests.[42,43] Ongoing studies that are evaluating the screening journey for participants choosing this blood-based test will inform questions on participant follow-up with diagnostic colonoscopy.[37-41] In addition, future work that involves health economic and outcomes modeling could inform the effect of this blood-based test on colorectal cancer–related outcomes, specifically the effect of a test with high adherence and lower sensitivity for advanced precancerous lesions than stool-based testing, and could assess whether the 3-year interval of the blood-based test, proposed by the manufacturer for screening, yields beneficial clinical outcomes. Future studies to understand the effect of longitudinal testing on sensitivity for advanced neoplasia warrant consideration.

In this study, the percentage of participants with an invalid cfDNA blood-based test result was 3.7% (298 of 8159) and within the target range (<5%) proposed for programmatic FIT offering.[44] Evaluating this percentage in the real-world setting will be important to understand population effect. Given the increasing incidence of colorectal cancer among persons younger than 45 years of age, understanding the potential clinical and health economic effect of a blood-based testing strategy to expand the screening age will be of interest.

In an average-risk screening population, this cfDNA blood-based test showed performance metrics of 83% sensitivity for the detection of colorectal cancer, 90% specificity for advanced neoplasia, and 13% sensitivity for advanced precancerous lesions.

Supported by Guardant Health.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank Deborah Fisher, M.D., M.H.S., and Kathryn Lang, M.B., B.S., for their contributions in the early phases of the study design and execution and Lucile Ryckebusch, of the contract research organization NAMSA, for writing assistance with an earlier version of the manuscript.

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